PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 59167-A-PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/22060	International filing date *(day/month/year)* 11 AUGUST 2000	Priority date *(day/month/year)* 13 AUGUST 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13 MARCH 2001	27 SEPTEMBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer SHIN-LIN CHEN
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Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/22060

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-70, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the claims:
pages 71-75, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the drawings:
pages 1-35, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the sequence listing part of the description:
pages 1-5, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[X] contained in the international application in printed form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/22060

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-33	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	4, 5, 15, 16, 18	YES
	Claims	1-3, 6-14, 17, 19-33	NO
Industrial Applicability (IA)	Claims	1-33	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-3, 6-14 and 27-33 lack an inventive step under PCT Article 33(3) as being obvious over Gayle et al., 1998 in view of GenCore Accession No. WO4334, 1996.

Claims 1-3, 6-14 and 27-33 are directed to a method for treating or preventing stroke or treating ischemic disorder in a subject comprising administering a CD39 polypeptide, such as soluble CD39 (SEQ ID No. 2), or an active fragment comprising 1-50 amino acids or 20-80 amino acids of SEQ ID No. 1, that inhibits ADP-mediated platelet aggregation. The claims further are drawn to administering the CD39 polypeptide or its active fragment prior to, at the onset of, or after stroke at various dosages, such as 1-20 mg/kg or 4-8 mg/kg of the subject's body weight.

Gayle teaches a soluble form of CD39, which is an ecto-enzyme with ADPase and ATPase activities, blocks ADP-induced platelet aggregation in vitro, and inhibits collagen-induced platelet reactivity. Gayle also suggests the soluble form of CD39 with full ADPase activity might constitute a novel approach to prevention and/or treatment of thromboembolic disease including stroke (e.g. abstract, introduction, p. 1857). Gayle does not teach the presence of CD39 having the sequence of SEQ ID No. 1 or 2.

GenCore Accession No. WO4334 presents a polypeptide sequence that is 100% identical to SEQ ID No. 1 or 2, and said polypeptide sequence is a human lymphoid cell activation antigen CD39 and could be used in reduction of platelet aggregation and of thrombogenicity.

It would have been obvious for one of ordinary skill at the time of the invention to use the CD39 polypeptide as taught by GenCore Accession No. WO4334 to prevention and/or treatment of thromboembolic disease including stroke as taught by Gayle because it was known that CD39, which is an ecto-enzyme with ADPase and ATPase activities, blocks ADP-induced platelet aggregation in vitro, and inhibits collagen-induced platelet reactivity. It would have been obvious for one of ordinary skill to administer a compound prior to, at the onset of, or after stroke at various dosages in the method taught by Gayle because they are routine optimization of result-effective variables and (Continued on Supplemental Sheet.)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The description is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 5 because it fails to adequately enable practice of the claimed invention because:

The description of the present application only discloses that CD39/ecto-ADPase inhibits thrombosis and limits ischemic cerebral injury in wild type and reconstituted nude mice. The scope of the claims include any active fragment of CD39 polypeptide, such as various mutated or truncated form of CD39 polypeptide, that could be used for treating or preventing stroke or treating ischemic disorder in a subject susceptible to intracranial hemorrhaging.

The description of the present application fails to provide adequate guidance and evidence for the function of various mutated or truncated form of CD39 polypeptide and the use of said mutated or truncated form of CD39 polypeptide for treating or preventing stroke or treating ischemic disorder. The biological function of a mutated or truncated form of CD39 polypeptide could differ dramatically from that of CD39 polypeptide. The amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the anti-platelet aggregation activity is lacking, it would be unpredictable whether any mutated or truncated form of CD39 polypeptide would still retain the anti-platelet aggregation activity of CD39 polypeptide and provide therapeutic effect for treating or preventing stroke in a subject. Thus, one skilled in the art at the time of the invention would not know how to use the claimed active fragment of CD39 polypeptide (SEQ ID No. 1) for treating or preventing stroke or treating ischemic disorder in a subject and require undue experimentation to practice over the full scope of the invention claimed.

Claims 1-16 and 26-33 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): A01K 67/00, 67/033; A61K 38/43; C07K 1/00; C12N 9/00 and US Cl.: 424/94.1; 435/183; 514/2; 530/348.25; 800/8, 9, 13, 18

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):
is obvious to a person of ordinary skill.

Claims 17 and 19-26 lack an inventive step under PCT Article 33(3) as being obvious over Guth et al., 1997 in view of Gayle et al., 1998.

Claims 17 and 19-26 are directed to a method for determining whether a compound inhibits platelet aggregation by increasing ADP catabolism so as to treat or prevent thrombotic or ischemic disorders in a subject by using an animal model and measuring platelet deposition, fibrin deposition, bleeding time, or infarction volume. The claims further are drawn to administering a compound prior to, at the onset of, or after stroke and a pharmaceutical composition comprising the compound identified, such as a CD39 polypeptide or an active fragment thereof.

Guth teaches using a BIBU52, a nonpeptide molecule, to block GPIIb/IIIa receptor so as to inhibit platelet aggregation both in vitro and in vivo animal models including guinea pig, pigs, and marmoset monkeys. Guth induces thrombus by damaging aorta with a hemostatic clamp and measuring the rate of thrombus formation, bleeding time, or mean blood-flow velocity with or without the administration of the compound BIBU52. Guth does not teach using CD39 polypeptide to inhibit platelet aggregation.

Gayle teaches a soluble form of CD39, which is an ecto-enzyme with ADPase and ATPase activities, blocks ADP-induced platelet aggregation in vitro, and inhibits collagen-induced platelet reactivity. Gayle also suggests the soluble form of CD39 with full ADPase activity might constitute a novel approach to prevention and/or treatment of thromboembolic disease including stroke (e.g. abstract, introduction, p. 1857).

It would have been obvious for one of ordinary skill at the time of the invention to use the CD39 polypeptide taught by Gayle to test its ability in inhibiting platelet aggregation in in vivo animal models as taught by Guth and be able to identify CD39 polypeptide could inhibit platelet aggregation by increasing ADP catabolism so as to treat or prevent thrombotic or ischemic disorders in a subject because of the teaching of Gayle. It would have been obvious for one of ordinary skill to administer a compound prior to, at the onset of, or after stroke in the method taught by Guth because they are routine optimization of result-effective variables and is obvious to a person of ordinary skill.

Claims 4, 5, 15, 16 and 18 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or f airly suggest having IL-2 as CD39 leader sequence, using saline, liposome, or anti-stroke agent as a carrier, or using a CD39-deficient mouse as an animal model.

---------- NEW CITATIONS ----------
NONE